A STUDY OF QUINOLINE COMPOUNDS

A THESIS

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Master of Science in Chemistry

by

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Approved:

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ACKNOWLEDGMENTS

On completion of this work I wish to express my deepest gratitude to Dr. P. K. Calaway, not only for his suggestion of the problem, but also for his most valuable aid and encouragement during its prosecution. I should also like to thank other members of the Department of Chemistry for their active interest and cooperation in making it possible for me to pursue this study.

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THE FRIEDLAENDER REACTION

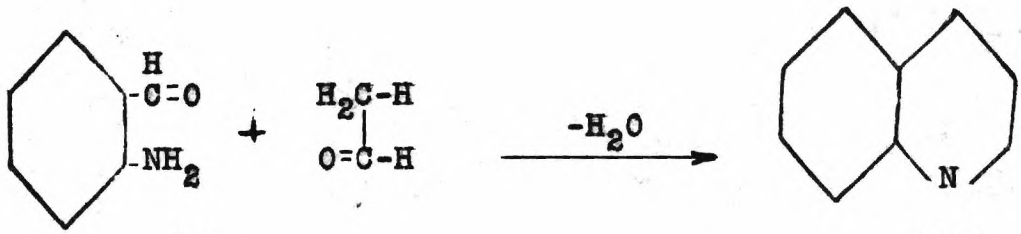
A STUDY OF QUINOLINE COMPOUNDS

CHAPTER I

THE FRIEDLAENDER REACTION

Friedlaender[1] in 1882 introduced one of the most important methods for the preparation of quinolines. Previously, Skraup[2] had prepared quinolines substituted in the benzene ring by the reaction of glycerol with anilines in the presence of sulfuric acid. The yields were poor and mixtures were usually obtained.

Friedlaender reacted o-amino-benzaldehyde (I) with acetaldehyde. The temperature of the reaction was maintained between 40 and 50 degrees Centigrade and a trace of sodium hydroxide was present. The following is the mechanism of the reaction:



(I) (II)

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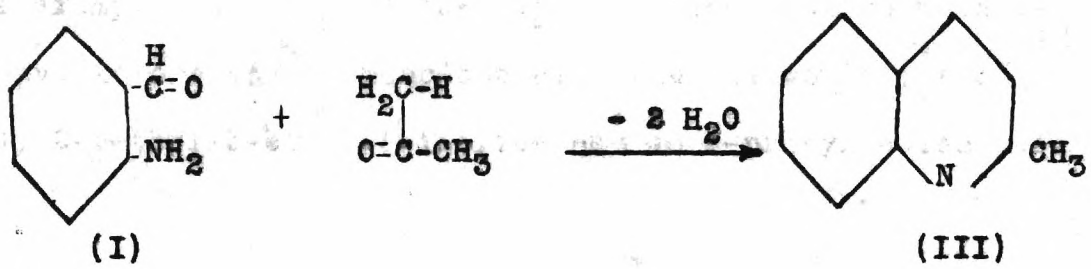
[1] Friedlaender, Ber., 15, 2572 (1882)

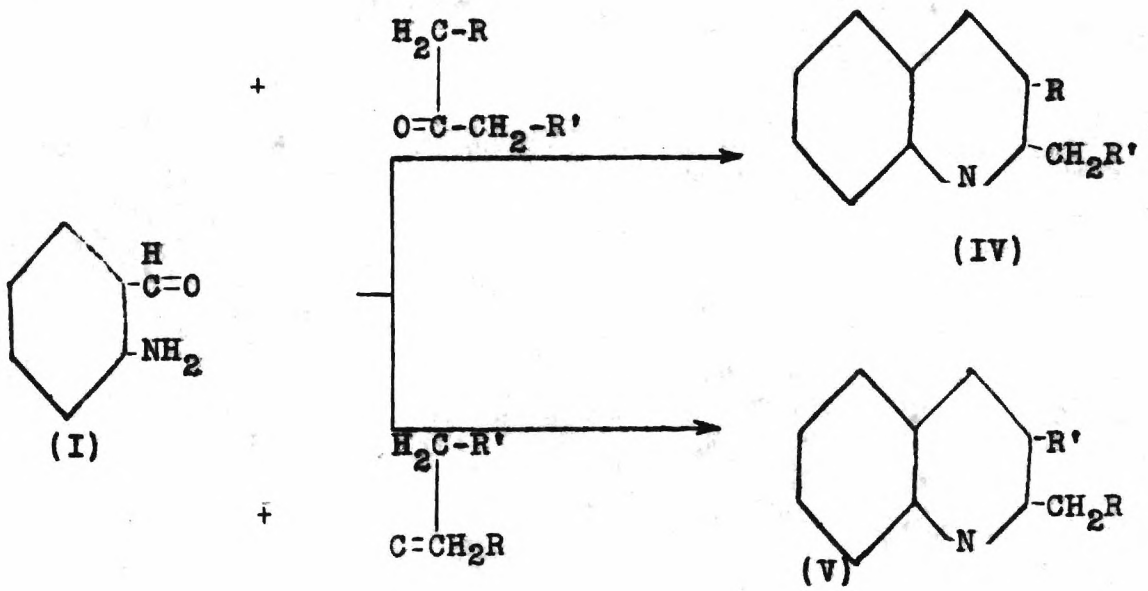
[2] Skraup, Monatsh., 2, 139 (1881)

In 1883 Friedlaender and Gohring[3] condensed o-amino-benzaldehyde (I) with methyl ketone to yield quinaldine (III). The mechanism proposed is as follows:



(I) (III)

Thus, it was seen that a good method for preparing quinolines was available with substitution taking place in the 2- and 3-positions. However, with unsymmetrical ketones it was observed that two compounds might result. The possible reactions are shown below:



(I) (IV) (V)

[3] Friedlaender and Gohring, Ber., 16, 1835 (1882)

Friedlaender and Eliasberg[4] showed that with unsymmetrical methyl ketones the reaction occurred to form only quinolines with the methyl group substituted in the 2-position. For example, they found that the reaction between methyl-propyl-ketone and o-amino-benzaldehyde (I) would yield only 2-methyl-3-ethyl-quinoline and no 2-propyl-quinoline.

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[4] Friedlaender and Eliasberg, Ber., 25, 1752 (1892)

CHAPTER II

THE PFITZINGER REACTION

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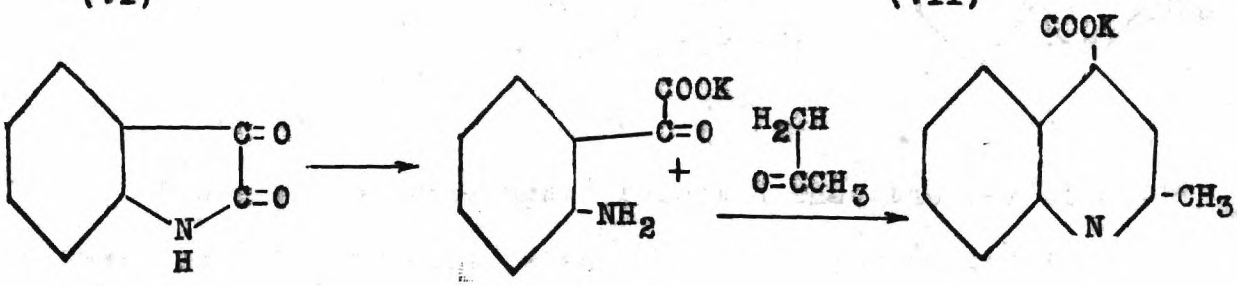
THE PFITZINGER REACTION

The preparation of quinoline derivatives starting with isatin (V(), a relatively inexpensive reagent, may be attributed to Pfitzinger.[1,2] He prepared 2-methyl-cinchoninic acid (VII) by the condensation of isatin (VI) with methyl ketone in the presence of 33 per cent aqueous potassium hydroxide.

(VI) (VII)



Through the same type of reaction using aldehydes, one might expect to synthesize cinchoninic acids substituted in the 2-position. Ketones might be expected to yield isomers substituted in the 2- and 3-position if the ketones are unsymmetrical. An illustration is afforded by the reaction between isatin (VI) and the ketone RCH_2CO-

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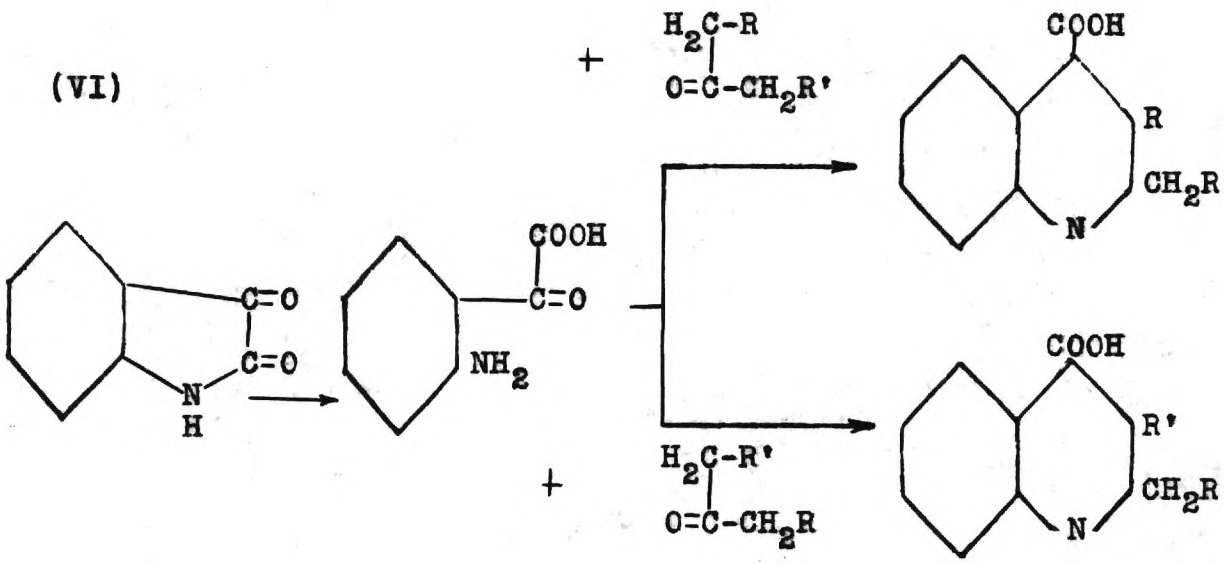
[1] Pfitzinger, J. prakt. Chem., 33, 100 (1886)

[2] Pfitzinger, J. prakt. Chem., 38, 582 (1888)

CH_2R' where R is any alkyl or aryl group and R' is an alkyl, aryl, or hydrogen radical. The mechanism of the reaction was formulated as follows by Halberkann[3]:



Thus, while Pfitzinger[4] reported that the reaction between methyl-ethyl-ketone and isatin (VI) resulted in 2,3-dimethyl-cinchoninic acid (VIII), it was later demonstrated that a small amount of 2-ethyl-cinchoninic acid (IX) was produced.[5]

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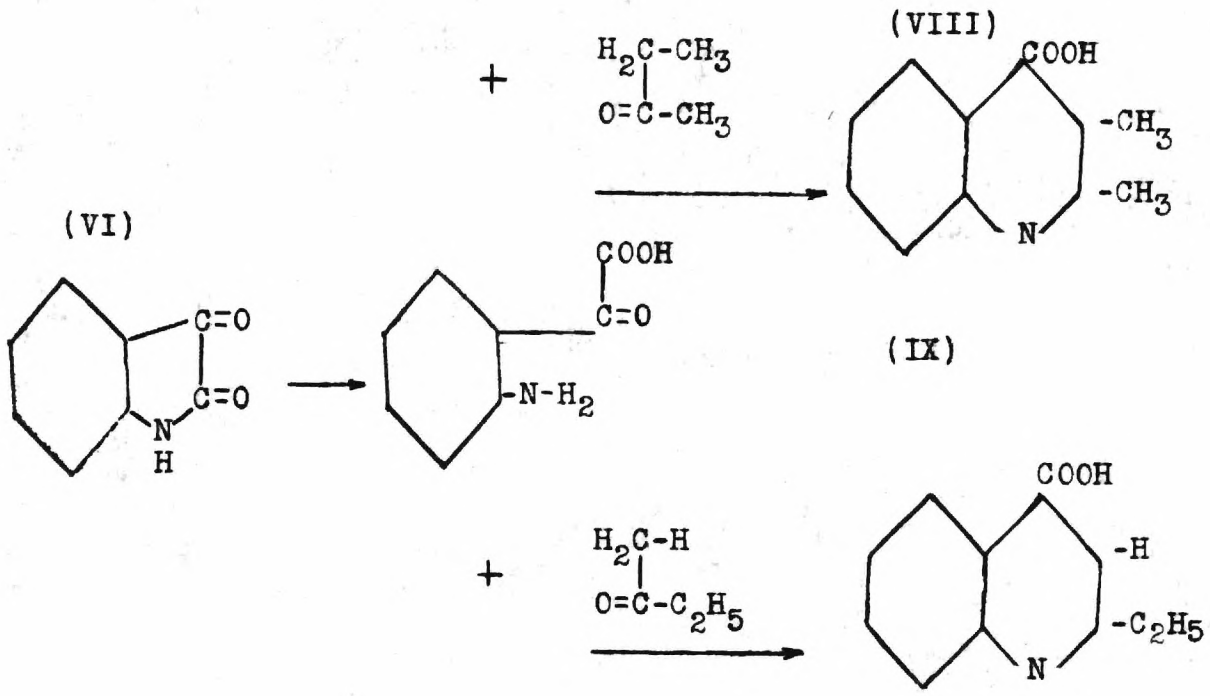
[3]Halberkann, Ber., 54, 3090 (1921)

[4]Pfitzinger, J. prakt. Chem., 56, 283 (1897)

[5]Von Braun, Gmelin, and Schultheiss, Ber., 56, 1344 (1923)



The general rule to follow is that in the Pfitzinger synthesis using unsymmetrical ketones the chief product of the reaction will have the smaller group affixed to the 2-position.

A modification of the Pfitzinger method was introduced in 1939 in which aryloxy ketones were used in place of the usual aliphatic and aromatic ketones.[6] The mechanism of the reaction showing the main product is shown on the following page.

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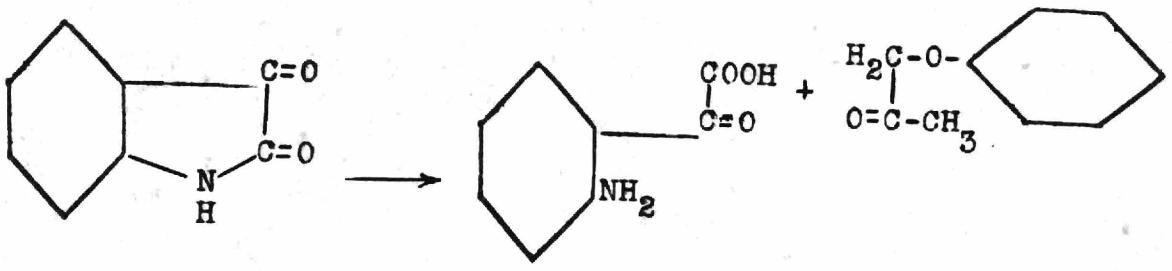
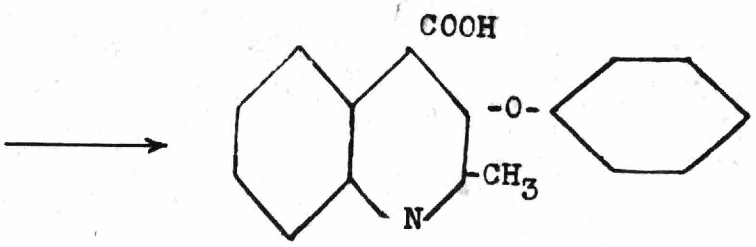
[6] Calaway and Henze, J. Am. Chem. Soc., 61, 1355 (1939)


C=O
C=O
N
H
COOH
C=O
NH2
+
H2C-O-
O=C-CH3


COOH
-O-
-CH3
N

CHAPTER III

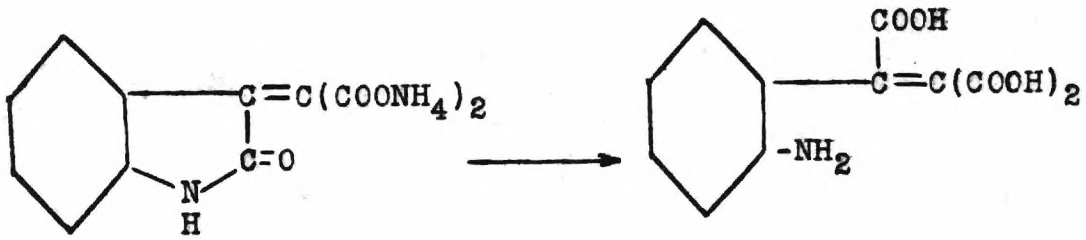
THE CONDENSATION OF MALONAMIDE AND ISATIN

CHAPTER III

THE CONDENSATION OF MALONAMIDE WITH ISATIN

The condensation of malonamide and isatin (VI) has been studied by Lindwall and Hill.[1] The reaction was carried out in a 3 per cent anhydrous alcoholic ammonia solution. From the analysis of the ammonium and silver salts the product reported was 3-(di-formamido)-ethylene-oxindole. Hydrolysis of the ammonium salt (X) produced 2-hydroxy-cinchoninic acid (XI). This structure was based on the analysis of the ethyl ester and a mixed melt with a known sample of ethyl-2-hydroxycinchoninate. The proposed reaction mechanism is shown below:

(X)



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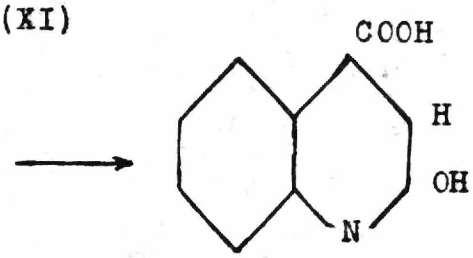
[1] Lindwall and Hill, J. Am. Chem. Soc., 57, 735-7 (1935)

(XI)



Treatment of 2-hydroxy-cinchoninic acid (XI) with hydroiodic acid and red phosphorous gave 1,2,3,4-tetrahydro-4-quinolone-carboxylic acid.

CHAPTER IV

PURPOSE OF THIS INVESTIGATION

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The search for substitutes for quinine has held the attention of numerous laboratories for several years. A synthetic anti-malarial would be a warmly-received addition to the pharmacopeia.

Biological experiments have proved that the quinoline group in quinine possesses marked anti-malarial properties. Research along this line has borne some fruit as quinoline derivatives have come into limited medical use as anti-malarials and specifics for various therapeutic applications. Plasmoquin is notable among this class of compounds.

It is hoped that the products obtained in this laboratory may in some manner add to the present knowledge concerning quinoline derivatives or provide a compound worthy of physiological research.

CHAPTER V

EXPERIMENTAL

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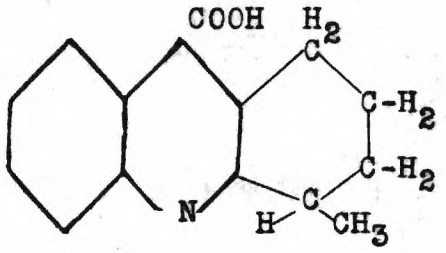
EXPERIMENTAL

The Preparation of 1-methyl-1,2,3,4-tetrahydro-10-acridinecarboxylic acid (XIII)



Twenty-nine and a half grams of isatin (0.2 mol) was dissolved in an excess of 33 per cent of aqueous ammonium hydroxide solution and placed in a 500 ml three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser. The mixture was heated to reflux on a water bath and 22.4 g (0.2 mol) of o-methylcyclohexanone was added over a period of three hours with continuous agitation. Reflux was continued for an additional twelve hours, the solution cooled in an ice bath, and neutralized with dilute acetic acid (Plate I). The yield of the crude acid was 26.0 g representing a theoretical yield of 54 per cent. The white compound was purified by treatment of the basic solution with Nuchar

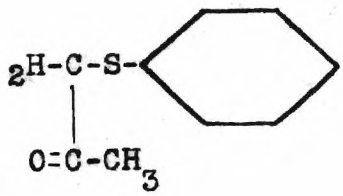
and precipitating the quinoline by neutralizing the clarified solution with dilute acetic acid.

The melting point of the compound was 278.3 degrees C. (corr.)

The neutral equivalent was found to be 258.2. Since the calculated molecular weight for the compound is 241 it was assumed that one molecule of water of crystallization was present bringing the theoretical weight to 259. The isomeric acids were obtained from aqueous solutions with one molecule of water of crystallization.[1]

The nitrogen content was found to be 5.52 per cent checking fairly well the percentage of 5.41 calculated for $C_{15}H_{15}O_2N \cdot H_2O$.

The Preparation of Thiophenoxyacetone[2,3,4]



[1] Borsche, Ann., 377, 119 (1910)

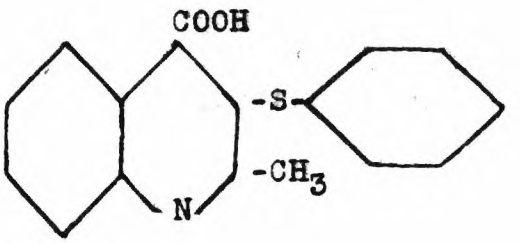
[2] Deslisle, ibid., 260, 252 (1890)

[3] Otto and Rossing, Ber., 23, 756 (1890)

[4] Authenreill, ibid., 24, 164 (1891)

Forty-five grams (0.5 mol) of thiophenol in benzene solution was placed in a three-necked one-liter flask fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser. Eleven and one-half grams (0.5 mol) of finely divided sodium was added with efficient stirring. After several days the sodium dissolved and sodium thiophenolate separated out as a white solid. Forty-six and three-tenths grams (0.5 mol) of chloroacetone was added slowly. After twenty hours refluxing, the sodium chloride was filtered from the mixture and the benzene removed by evaporation. The resulting thiophenoxyacetone was fractionated and the portion boiling between 160 and 165 degrees C. at 35 to 40 mm pressure was collected. The oil solidified upon cooling and was recrystallized from alcohol. The melting point (uncorr.) was 34 degrees C. agreeing closely with the literature. The yield was 56.5 g or 68 per cent of theoretical.

The Preparation of 3-thiophenoxy-4-quinaldinecarboxylic acid (XIV)



Twenty-eight and seven-tenths grams (0.195 mol) of isatin (VI) was dissolved in 175 ml of 33 per cent aqueous potassium hydroxide solution in a 500 ml Erlenmeyer flask and 32.4 g (0.195) mol) of thiophenoxyacetone was added. (plate III). The mixture was refluxed over a water bath for twenty-three hours and treated with Nuchar. The clarified solution was cooled in ice and neutralized with dilute acetic acid. The white crystals separating out were recrystallized from ethyl alcohol and dried in an oven.

The yield was 62.4 per cent of the theoretical. The compound melted at 285-6 degrees C. (corr.) (dec.)

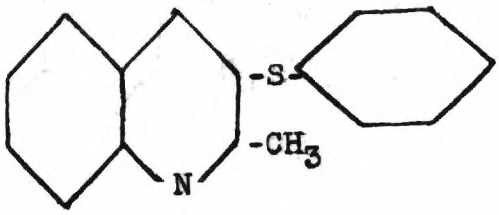
A quantitative nitrogen analysis showed 4.90 per cent as compared with the theoretical value of 4.75.

A sulfur determination by the oxygen bomb washing method showed 10.60 per cent. Theoretically the sulfur content should have been 10.84 per cent.

The neutral equivalent was determined as 291.2. The calculated molecular weight was 295.

Cleavage of the thioether linkage was attempted by heating the compound (XIV) with concentrated hydrochloric acid in a Carius furnace for thirteen hours at 140 degrees C. Only partial decomposition was obtained.

The Preparation of 3-thiophenoxyquinaldine (XV)

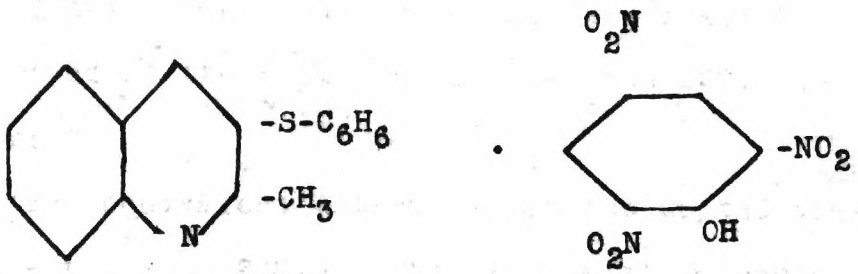


Ten grams of 3-thiophenoxy-4-quinaldinecarboxylic acid (XIV) was distilled under diminished pressure. Carbon dioxide was evolved and a pale brown distillate was collected. The odor of thiophenol was evident. The liquid was redistilled under 40-50 mm pressure and the portion boiling between 250-256 degrees C. was retained. The light colored liquid was washed with dilute sodium hydroxide and after several recrystallizations the melting point became constant at 67.8 degrees C. (corr.)

Analysis of the compound showed 6.18 per cent nitrogen; the theoretical percentage was 5.57.

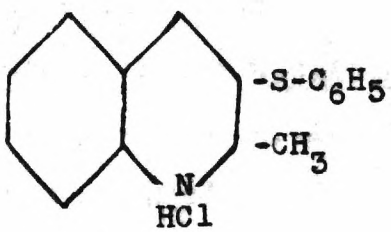
Sulfur analysis revealed 12.52 per cent sulfur, whereas the theoretical percentage was 12.73.

The Preparation of the Picrate of 3-thiophenoxyquinaldine (XVI)



A small amount of 3-thiophenoxyquinaldine (XV) was dissolved in alcohol and an alcoholic solution of picric acid was added. The picrate immediately separated out as a deep yellow precipitate. The substance when recrystallized from alcohol showed a melting point of 200-201 degrees C. (corr).

The Preparation of the Hydrochloride of 3-thiophenoxyquinaldine (XVII)



The hydrochloride of 3-thiophenoxyquinaldine (XV) was prepared by passing dry hydrogen chloride gas through

a benzene solution of the quinaldine. The white hydrochloride separated out of the benzene solution as a solid. The melting point of the purified compound was 200.5 degrees C. (corr.)

A neutral equivalent determination run on the compound showed a value of 288.0. The calculated molecular weight of the compound was 287.6.

The Preparation of the Malonamide-Isatin Product (XVIII)

Twenty-nine and four-tenths grams (0.2 mol) of isatin (VI) and 20.4 g (0.2 mol) malonamide were dissolved in an excess of ammonium hydroxide solution. In a few minutes a brownish-yellow precipitate settled out. After forty-eight hours standing the solid material was filtered and washed with water through a Buchner funnel. The dried product weighed 36.5 g. The compound when recrystallized from nitrobenzene showed signs of sublimation at 240 degrees C. At 249 degrees some decomposition had taken place.

The literature showed that Lindwall and Hill[5] had prepared a compound from malonamide and isatin in an anhydrous alcoholic ammonia solution. As previously stated, they believed their product to be 3-(di-formamido)-ethy-

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[5]Lindwall and Hill, J. Am. Chem. Soc., 57, 735-737 (1935)

lene-oxindole. This substance was reported to have a definite milting point of 245 degrees C., was soluble in alcohol and benzene, and crystallized out of nitrobenzene in yellow plates.

The compound prepared in our laboratory with ammonium hydroxide as the reaction solvent differed in color and melting point from that reported by Lindwall and Hill. Our compound showed no evidence of unsaturation and gave a positive ferric chloride test, indicating the presence of an enol or phenol group. The product was also sparingly soluble in water and in the more common organic solvents.

In mineral acids the compound dissolved giving a deep red coloration and precipitating as a fine yellow crystalline product with the evolution of ammonia.

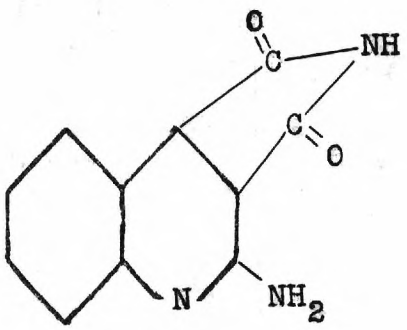
In 33 per cent potassium hydroxide solution the substance turned red with the evolution of ammonia and was finally converted into a yellowish material which later dissolved. The neutralized solution yielded a white precipitate.

Molecular weight determinations failed due to the insolubility of the compound in available solvents.

An attempted neutral equivalent determination proved futile because of the apparent hydrolysis of the substance.

Sublimation Product from Malonamide-Isatin Product (XIX)

A small amount of a bright yellow substance was collected as the sublimate by the sublimation of a few grams of the malonamide-isatin product (XVIII) using the apparatus of Bailey.[6] When recrystallized from alcohol the compound showed a sublimation point of 250 degrees C. A Gabriel reaction showed evidence of an imide structure, but such small quantities were used that the amine produced could not be isolated. The percentage nitrogen found in the material was 19.84. So far the structure of the compound has not been established, but the following is a possible formula:

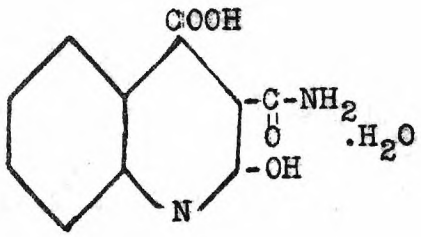


[6] Bailey, Ind. Eng. Chem., Anal. Ed., 12, 194 (1940)

Compound from Treating the Malonamide-Isatin Product with Hydrochloric Acid (XX)

The original malonamide-isatin product (XVIII) was treated with concentrated hydrochloric acid in a reflux apparatus for several hours and a yellow crystalline compound separated out. The compound when recrystallized from alcohol showed a melting point of 358 degrees C. (corr.)

The observed nitrogen percentage was 11.04. One possible formula for the yellow compound from hydrochloric acid (XX) is shown below:



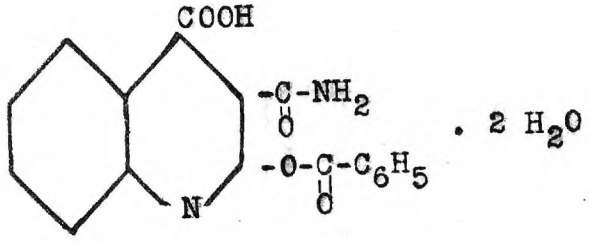
This compound has a nitrogen percentage of 11.08.

Treatment with strong potassium hydroxide solution and subsequent neutralization resulted in the formation of a white substance which had all the properties of the compound (XXII) obtained by treating the original malonamide-isatin product (XVIII) with potassium hydroxide solution.

The Preparation of the Benzoyl Ester of the Preceding Compound (XXI)

A benzoyl ester was prepared in a pyridine solution using benzoyl chloride. The crystals from alcohol solution were deep yellow in color. They showed no definite melting point, but darkened at 180 degrees C.

The percentage nitrogen observed was 7.35. This compared favorably with the calculated percentage of 7.52 for the following structure.

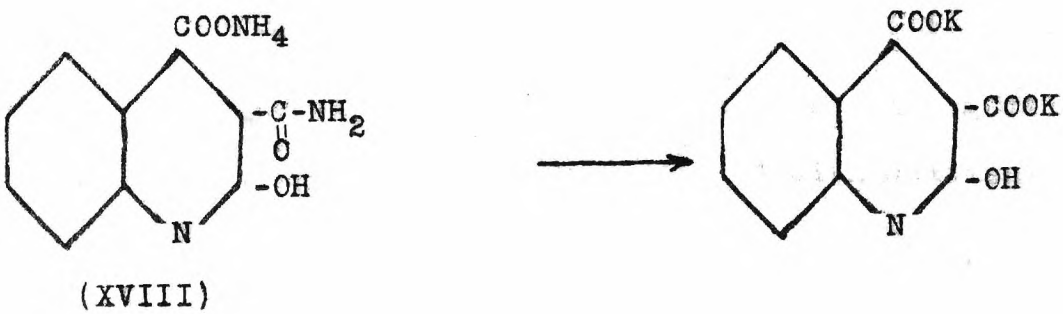


The Product Obtained from the Action of Potassium Hydroxide on the Malonamide-Isatin Product- (XXII)

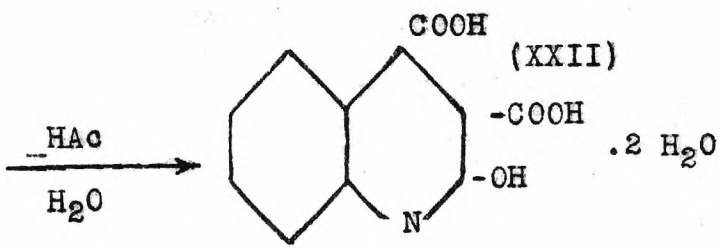
The white solid previously described as coming out of the malonamide-isatin (XVIII) upon treatment with 33 per cent potassium hydroxide was somewhat soluble in water and very soluble in bases. It melted at very high temperature with decomposition as evidenced by spatula tests.

Ferric chloride tests produced a red coloration indicating the presence of enol or phenol groups.

A possible reaction mechanism is as follows:



(XVIII)



A neutral equivalent determination produced the value of 133.9. For two carboxyl groups the molecular weight would be 267.8. The above compound theoretically has the molecular weight of 269.

The nitrogen percentage observed for the compound was 5.21. For the above formula the calculated percentage would be 5.20.

An attempt was made to decarboxylate the compound by heating with slaked lime. At a very high temperature water was given off due to the decomposition of the lime.

Carried over with the water was a soluble brownish-yellow material possessing a disagreeable odor. The solution was picrated yielding a deep red solid material melting into a liquid at 178 degrees C. These properties indicated the formation of indole.[7] It was assumed that the hydrolysis compound (XXII) was completely decarboxylated giving carbostyril which yielded indole when heated with calcium hydroxide. According to Mulliken[8] carbostyril when heated with a solid base is converted to indole.

A resume of the work undertaken with the product from malonamide and isatin and the subsequent derivatives may be found on Chart V. It is freely admitted that conclusive proof for the structure of some of the compounds cannot be presented with the information obtained, but it is hoped that the results gathered may help in the subsequent identification. The most probable configurations from the data obtained have been given in order that the future investigator may have some idea of the types of compounds studied.

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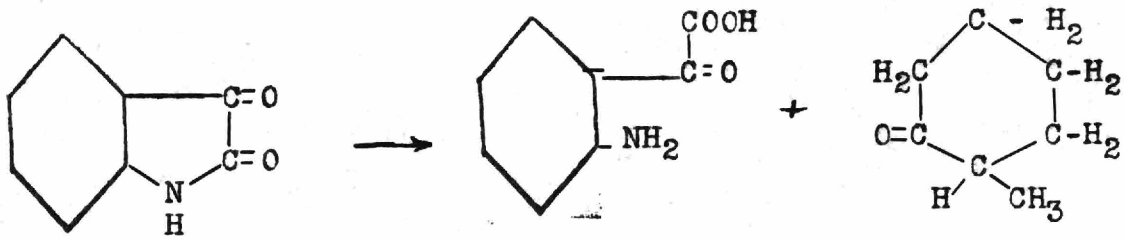
[7]Mulliken, The Identification of Pure Organic Compounds, II, 156.

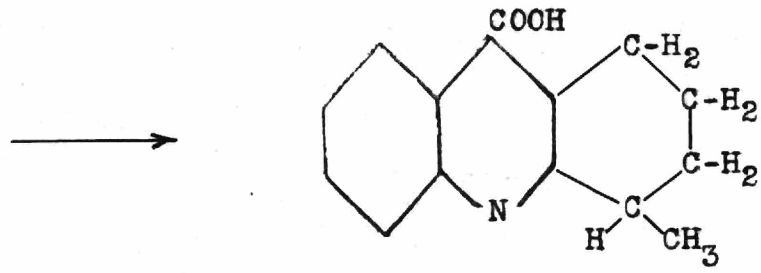
[8]Ibid., II, 209.

PLATE I

The Preparation of 1-methyl-1,2,3,4-tetrahydro-10-acridinecarboxylic acid (XIII)



(VI)



(XIII)

PLATE II

The Preparation of Thiophenoxyacetone

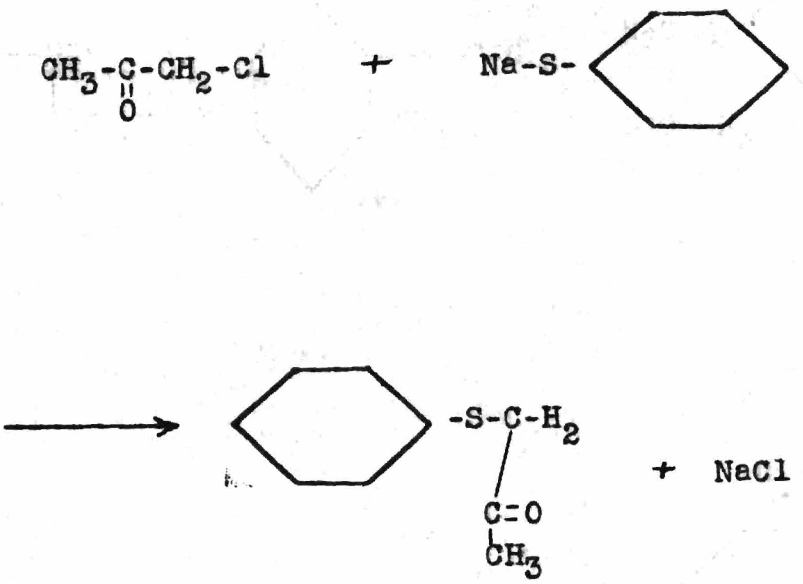
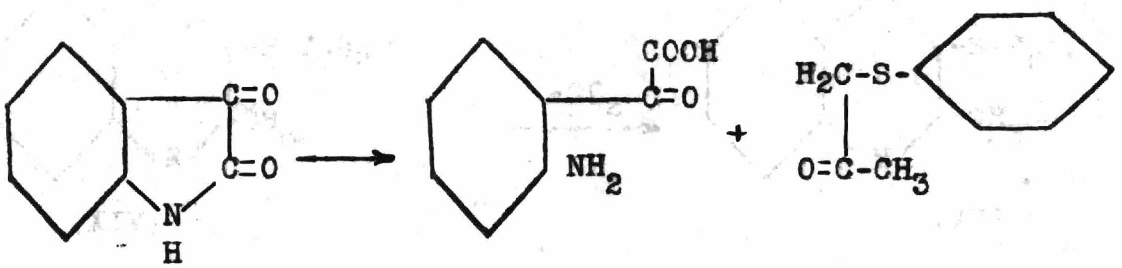
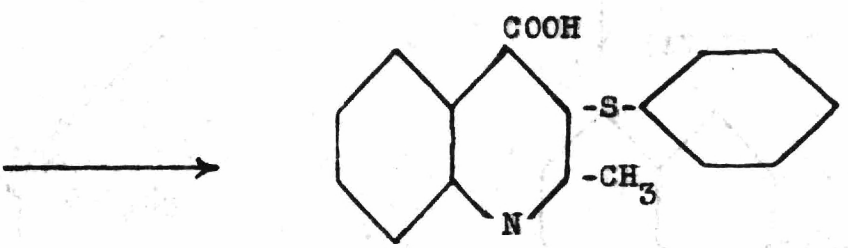


PLATE III

Reaction Between Isatin and Thiophenoxyacetone



(VI)



(XIV)

PLATE IV

Derivatives from 3-thiophenoxy-4-quinaldinecarboxylic acid

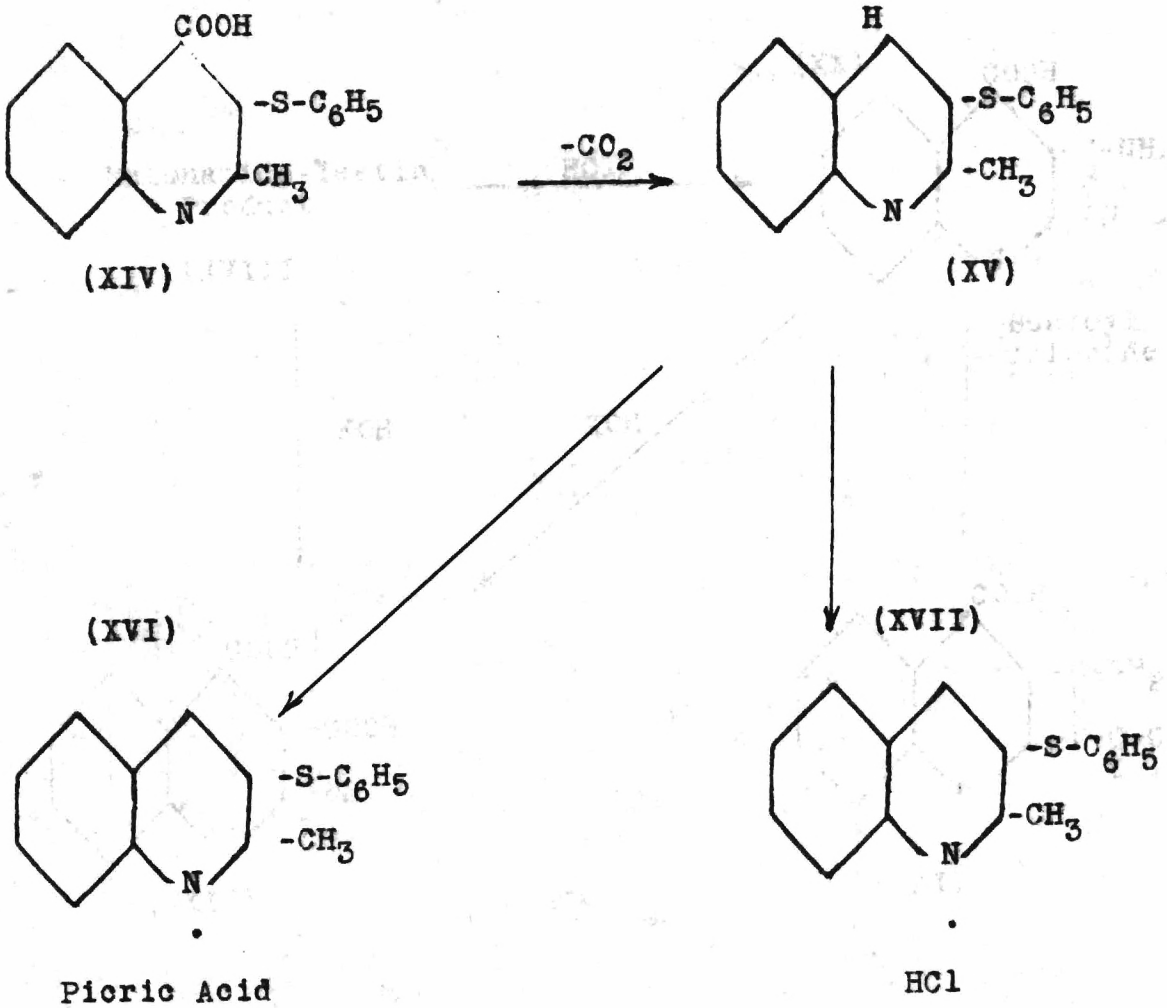
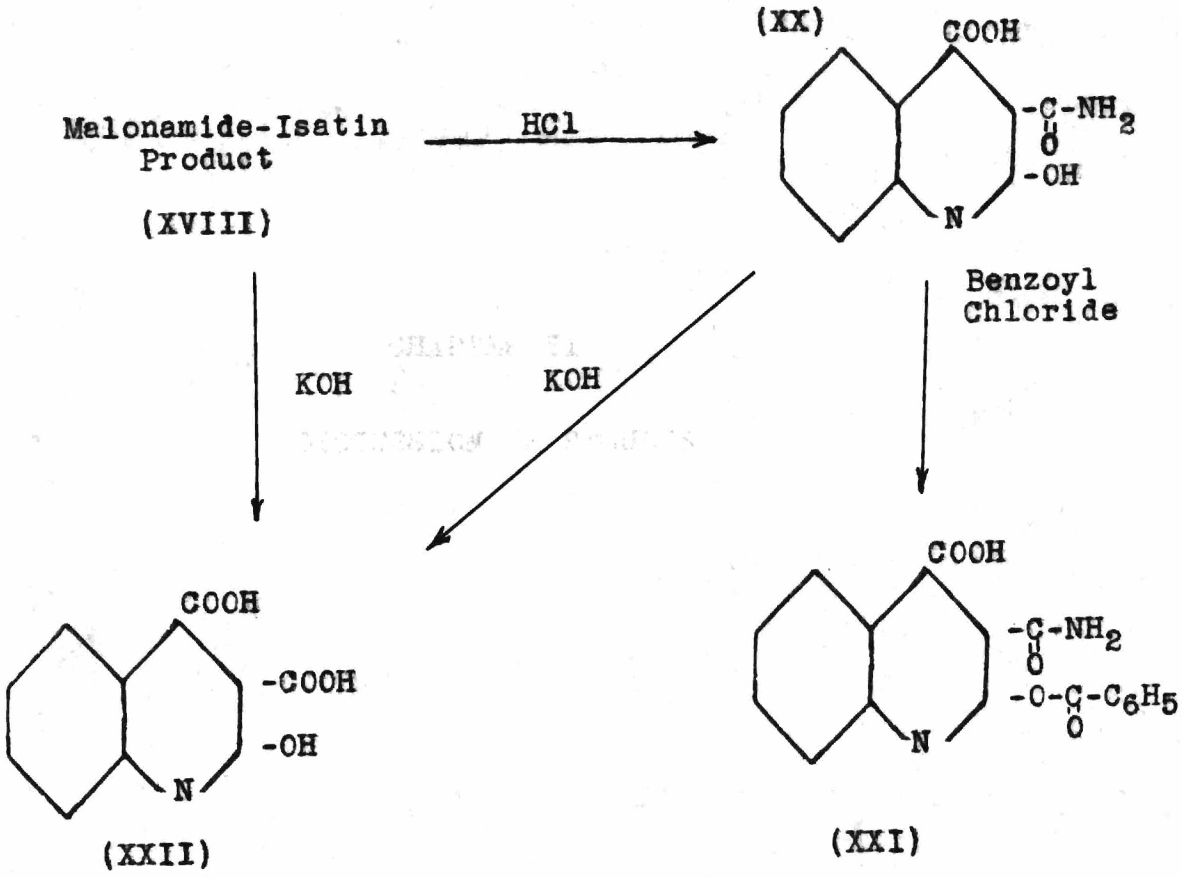


PLATE V

Derivatives of Malonamide-Isatin Product



CHAPTER VI

DISCUSSION OF RESULTS

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The feasibility of the use of the Pfitzinger reaction for the preparation of quinoline derivatives substituted in the 3-position by a thioaryl group has been demonstrated. The data obtained would definitely prove the formation of 3-thiophenoxy-4-quinaldinecarboxylic acid (XIV) and its decarboxylation to 3-thiophenoxyquinaldine (XV). Proof of the conversion of the latter compound to the picrate is herein concluded. The preparation of the hydrochloride of 3-thiophenoxyquinaldine may be substantiated by the neutral equivalent and other pertinent data included.

1-methyl-1,2,3,4-tetrahydro-10-acridinecarboxylic acid (XIII) has been prepared by a slight modification of the method reported by Borsche for the synthesis of isomeric acids.

The preparation of the product from malonamide and isatin (XVIII) supplies an interesting source of possible new compounds, but the complexity of the derivatives obtained tends to make the establishment of the structures a major task. It is reasonable to assume that the original compound obtained was distinct from that previously reported by Lindwall and Hill in that aqueous ammonium hy-

droxide was utilized instead of the anhydrous alcoholic ammonia solution they used for their reaction solvent. Of the derivatives of this compound the structure of one had been fairly well established. Compound (XXII) is believed to be 2-hydroxy-3,4-quinoline-dicarboxylic acid because of analytical data and observed reactions. The hydrolysis product from hydrochloric acid (XX) and its benzoyl ester (XXI) have been given structures in keeping with the information secured concerning them, but without definite proof that the entire molecule must have the configuration assigned to them.

Further investigations being pursued in this laboratory should complete the identification of the products obtained from the malonamide-isatin condensation.

CHAPTER VII

SUMMARY

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SUMMARY

The following compounds have been prepared and their chemical properties studied: 1-methyl-1,2,3,4-tatrahydro-10-carboxylic acid, thiophenoxyacetone, 3-thiophenoxy-4-quinaldinecarboxylic acid, 3-thiophenoxyquinaldine, the picrate and hydrochloride of 3-thiophenoxyquinaldine, and 2-hydroxy-3,4-quinoline-dicarboxylic acid.

Four more substances, numbered XVIII, XIX, XX, and XXI have been prepared and structures have been assigned to the last three in keeping with the chemical properties and analytical results observed.

The compound prepared by condensing isatin and malonamide in an ammonium hydroxide solution (XVIII) differed from the product reported by other investigators using an anhydrous alcoholic ammonia solution as the reaction solvent for the same reactants.

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